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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/781,384	02/18/2004	David Spencer	HO-P02165US1	2112

26271 7590 05/05/2006

FULBRIGHT & JAWORSKI, LLP
1301 MCKINNEY
SUITE 5100
HOUSTON, TX 77010-3095

EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 05/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/781,384	SPENCER ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending and under current examination.

Claim Rejections

Claim 13 is objected to because of the repeated recitation, "all operably linked".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 6-8, 13, 21, 23, 24 are rejected under 35 U.S.C. 102(a) as being anticipated by *Dicker et al* (WO 02/36769).

WO 02/36769 discloses a composition comprising a polynucleotide promoter sequence (CMV) operably linked to a polynucleotide encoding CD40 ligand-binding/trimerization domain and a polynucleotide sequence encoding CD40 intracellular signaling domain (figure in page 1, and page 23). WO 02/36769 teaches to further include a polynucleotide encoding a transmembrane domain of a type II receptor from TNF and TNF-related ligands (considered as a second ligand-binding region and a membrane-targeting sequence, e.g. last

paragraph, page 12) in the polynucleotide construct. WO 02/36769 teaches the composition could be used for activation of professional antigen-presenting cells (APCs) including dendritic cells in the same way as CD40 ligand to CD40 (e.g. paragraph bridging pages 3-4). WO 02/36769 goes on to teach the vector could be used as an essential component of a pharmaceutical composition (e.g. page 7, lines 14-18) or further including a mammalian host cell transfected with the expression vector as a pharmaceutical composition for enhancing immune response (e.g. page 6, lines 19-24). Accordingly WO 02/36769 anticipates instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-9, 11, 13-18, 20-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Dicker* (WO 02/36769), in view of *Nair et al* (USP 6,670,186).

WO 02/36769 discloses a composition comprising a polynucleotide promoter sequence (CMV) operably linked to a polynucleotide encoding CD40 ligand-binding/trimerization domain and intracellular CD40 signaling domain (the figure in page 1, and page 23). WO 02/36769 teaches further including a polynucleotide encoding a transmembrane domain of a type II receptor from TNF and TNF-related ligands (e.g. last paragraph, page 12). WO 02/36769 teaches the composition could be used for activation of professional antigen-presenting cells (APCs) including dendritic cells in the same way as CD40 ligand to CD40 (e.g. paragraph bridging pages 3-4), and thus implicitly suggested the use of CD40 ligand. WO 02/36769 goes on to teach other co-stimulatory factor could be included in the composition such as B-7, IL-12, etc. (e.g. tables 1-2), which can be constructed in the same vector or on different expression vectors (page 5, 3rd paragraph). WO 02/36769 also teach using such for enhancing anti-tumor immune response, wherein the vector could be directly introduced into tumors (where antigen-presenting cells are present and thus transfected) by intradermal gene gun (page 13, 2nd paragraph), or introduced after transfecting tumor cells *in vitro*, and thus the composition would be administered simultaneously with an immunogenic composition (tumor antigens on tumor cells, e.g. working examples).

Although WO 02/36769 does not mention loading APCs with tumor antigen antigenic peptides, or mRNA of an antigen, such techniques had been routine in the art for activating APCs as taught by *Nair et al* (e.g. abstract, column 1, lines 29-41).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to first load APCs with antigens or nucleic acid encoding antigens *in vitro* before administering the transfected APCs to the host in need with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because antigen loading could maximize the activity of APCs *in vivo*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over *Dicker* (WO 02/36769), in view of *Nair et al* (USP 6,670,186) as applied to claims 1-4, 6-9, 11, 13-18, 20-23 above, further in view of *Shu* (US 2003/0082163).

The combined teachings of *Dicker*, in view of *Nair et al* were detailed above, which failed to teach electrofusing tumor cells for APCs loading. Shu supplemented the deficiency by illustrating the technique was well know in the art at the time of instant filing date. *Shu* teaches conventional loading of APCs with antigen is limited by the availability of chemically defined antigenic proteins, and discloses loading dendritic cells (APCs) with tumor cells in the manner of electrofusing resulting in fused DC-tumor cells. *Shu* teaches such cells contain all

essential DC molecules and express numerous tumor antigens, and is a powerful tool in eradiating tumor *in vivo* (e.g. abstract and paragraph 0011).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to load APCs by electrofusion with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the fused cells have more potent anti-tumor effect. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for activating an antigen-presenting cell comprising transfecting an antigen presenting cell *in vitro* with an expression vector, followed by administering the transfected APCs to a subject, wherein the expression vector comprises a polynucleotide encoding a CD40 molecule containing the cytoplasmic signaling domain, a chemical ligand-binding region of FK506, and a membrane-targeting protein (M-FvFvlsCD40-E) operably linked to a promoter, wherein the CD40 cytoplasmic domain and the chemical ligand-binding region forms a single functional unit so that a chemical ligand binding

event would trigger the CD40 signaling pathway and activate APCs; does not reasonably provide enablement for activating an antigen-presenting cell comprising transfecting an antigen presenting cell directly *in vivo* with an expression vector; does not reasonably provide enablement for activating APCs, wherein the vector encodes any ligand-binding region, any co-stimulatory polypeptide, or a CD40 polypeptide lacking the cytoplasmic domain; and it does not reasonably provide enablement for activating APCs, wherein the ligand-binding region(s) and CD40 molecule are separate functional units. The specification fails to teach how to use a second ligand-binding region, in the inducible CD40 molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided.

The claims are directed to a composition and a method of using such for transfecting an antigen-presenting cell, wherein the composition is an expression vector encoding a ligand-binding region, a CD40 molecule or any co-stimulatory polypeptide, and optionally another ligand-binding region. Given the broadest

reasonable interpretation, the claims are drawn to a therapeutic composition and method of using such for activating APCs and modulating immune response in vivo, and thus the claimed invention would be evaluated by such standard.

Given the broadest reasonable interpretation, the claims encompass a genus of vectors/methods of using such vectors having multitude combinations of at least one ligand-binding region for any protein or non-protein ligand, and either a CD40 molecule or any of variety of co-stimulatory polypeptides, which are *functionally capable* of activating an APC, and which are essential materials used in the method. However, the specification fails to provide an adequate disclosure for the genus of the claimed invention in terms of functional characteristics and structure-functional relationship of the genus constructs.

In view of instant disclosure, the specification contemplates various co-stimulatory polypeptides such as TNF family (§ A, page 21), various ligand-binding sequences (§ B, page 22), and membrane-targeting sequences (§ D, page 26); the specification exemplifies the concept by constructing an inducible CD40 receptor comprising a CD40 cytoplasmic signaling domain, tandem copies of the dimerizing drug-binding domain of FKBP12, and a myristoylation-membrane targeting domain. The specification teaches when exposed to a non-protein chemical dimerizer A20187, primary dendritic cells transfected by the iCD40 construct activate with stronger intensity and lasting effects compared to conventional stimuli such as LPS and CD40 ligand *in vitro* and *in vivo* (e.g. figs. 2E & 4A-E). However, the specification fails to teach whether the function of the exemplified vector mirrors that of the genus vectors.

In view of the state of the art, functional effects of different co-stimulatory polypeptides are not equal. For example, *Jacquot et al* (J Immunol 1997;159: 2652-7) teach when compared to the dramatic enhancement of B cell proliferation induced by CD40/CD40L, CD27/CD70 (another TNF receptor family member) only induced a slight increase in B cell proliferation. Further, CD40/CD40L, but not other TNF family members, was known to be a strong co-stimulatory molecule that is capable of serving the function as recited in the claims (*Tong et al*, Cancer Gene Therapy 2003;10:1-13). In fact, the specification provides evidence that only the disclosed iCD0 construct comprising the chemical ligand-binding region is capable of being a pharmaceutical composition for activating APCs because the conventional stimuli such as LPS, TNFα, anti-CD40 mAb, or CD40L only slightly or not at all triggered the signaling pathway of NFkB required for DC activation (e.g figure 2E). As such, the specification fails to provide an enabling disclosure for the other members of the TNF family, the Toll-like receptors, C-reactive protein receptors, Pattern recognition receptors, and HSP receptors as contemplated in the specification for activating antigen-presenting cells since in an unpredictable art, single disclosed species is often insufficient for the enablement of the genus.

Given the broadest reasonable interpretation, the claimed expression vector encompasses a vector encoding at least two unrelated components, a ligand-binding domain, and a CD40 molecule (or any co-stimulatory molecule), while administering a ligand would activate the transduced APCs. However, the specification fails to teach how the ligand binding to the ligand-binding region

could activate APCs if and when the CD40 is independent of the ligand-binding region(s). The specification only provides enablement when the ligand-binding region is part of the inducible CD40 receptor. It is acknowledged that claim requires all of the component links by one promoter, but the promoter does not necessarily links the function of the expression products.

Given the broadest reasonable interpretation, the claimed expression vector comprises multitude of polynucleotides encoding various ligand-binding regions and co-stimulatory molecules that form a single functional unit. This requires the structure of the end protein receptor product functions as expected. However, the specification fails to teach the structure-functional relationship of the functional unit.

In view of the state of the art in protein chemistry, it is probably one of the most unpredictable areas of biotechnology. Although the polynucleotide-coding region determines amino acid sequence of the protein, it is the conformation of three-dimensional structures that allows the protein to function and carry out the supposed activity such as signaling. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach certain position in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). One cannot extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structure of polypeptides encompassed by these claims and whether they can serve as a functional activator of APCs. *Rudinger* (Peptide Hormones 1976; June;pages 1-7) teaches the relationship of

sequence components and the peptide hormone function "THE SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY." (last paragraph of text on page 6). In fact, the instant specification provides evidence for such unpredictability. For example, the specification teaches, the construct M-CD40-FvFvIs-E, having the same component of M-FvFvIs-CD40-E, was less responsive to the chemical ligand AP20187, and thus only the M-FvFvIs-CD40-E is enabling as a pharmaceutical composition, and enabling for activating APCs and modulating an APC-mediated immune response.

Given the broadest reasonable interpretation, the claimed invention encompassing directly transfecting APCs *in vivo*. However, the specification fails to teach how to deliver the expression vector so that they could transfect sufficient numbers of APCs in vivo such that a pharmaceutical effect could be obtained. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired cells *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, *Deonarain* (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS FOR A LONG ENOUGH PERIOD OF TIME" (page 53, first paragraph). *Deonarain* teaches, "GENE DELIVERY REMAINS THE MAJOR TECHNOLOGICAL STUMBLING BLOCK IN GENE

THERAPY STRATEGIES", (2nd paragraph, page 54). The specification only enables administering transfected APCs for sufficient immune enhancing effect *in vivo*.

Therefore, in view of the limited guidance, the lack of predictability of the art, and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because claim 6 recites, "administering an expression vector, wherein said expression vector is expressed in dendritic cells". It is unclear, whether a vector or a transfected cell is administered, and thus the metes and bounds of the claims are uncertain.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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application file folder(s) as well as general patent information available to the public.

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Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
April 17, 2006